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Dobutamine Stress Echocardiography Early After Heart Transplantation Predicts Development of Allograft Coronary Artery Disease and Outcome

KWAME O. AKOSAH, MD, SUSAN McDANIEL, MD,* JOSEPHINE S. HANRAHAN, BS,*
PRAMOD K. MOHANTY, MD, FACC*

Richmond, Virginia and LaCrosse, Wisconsin

Objectives. **This study sought to determine the prognostic significance of serial dobutamine stress echocardiography (DSE) in new heart transplant recipients and to examine the relation between persistent wall motion abnormalities and the eventual development of coronary artery disease (CAD) as assessed by angiography.**

Background. **Allograft CAD is a major cause of graft failure. However, clinical diagnosis of the early disease remains difficult. The reasons for this include the diffuse nature of the disease and its predilection for the microvasculature, which are not easily detected by coronary angiography. Identifying patients at risk for the development of angiographic CAD early after transplantation may allow such patients to be targeted for aggressive treatment options to prevent subsequent cardiac events and early graft failure.**

Methods. **Twenty-two new heart transplant recipients were selected to undergo serial DSE at the time of their regularly scheduled endomyocardial biopsy. In addition, patients underwent scheduled annual coronary angiography. DSE was performed in 5-min stages with infusion of intravenous dobutamine at 5, 10, 20, 30 and 40 μg/kg body weight per min.**

Results. **Twenty-two patients had 91 DSE studies and 45 coronary angiograms. The patients were categorized into three groups based on the echocardiographic results. Group 1 (n = 7) had normal serial stress echocardiographic studies. Group 2 (n = 4) had transient inducible wall motion abnormalities. Group 3 (n = 11) developed persistent wall motion abnormalities. During a mean follow-up time of 32 ± 11 months (range 5 to 50), 8 (73%) of 11 patients in Group 3 developed events. The events included angiographic CAD (n = 7), myocardial infarction (MI) (n = 1) and cardiac death (n = 3). The patient who developed an MI had a normal coronary angiogram. No cardiac event or angiographic disease occurred in either Group 1 or 2 patients.**

Conclusions. **These results suggest that dobutamine-induced wall motion abnormalities, which are persistent in new heart transplant recipients, are predictive of the development of angiographic CAD, MI or death.**

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The etiology of graft failure after heart transplantation is multifactorial. Acute cellular rejection (1–3), vascular rejection (4,5), coronary artery disease (CAD) (6–8) and perioperative ischemic myocardial necrosis (9) have all been reported to contribute to cardiac allograft dysfunction. Among these, allograft CAD is the most prevalent condition that limits long-term graft survival (8). Allograft CAD may be an immune-mediated process with accelerated progression. The disease is typically silent and the diagnosis is often made at autopsy, especially in the early months after heart transplantation. The onset of allograft CAD may be diffuse, with a predilection for the microvasculature. By the time focal lesions are detected on the angiogram, the disease process is advanced and the treatment option is limited to retransplantation. Early detection of allograft CAD is therefore an important step in developing effective therapeutic modalities. The ability to identify patients who are at risk for developing angiographic disease early after heart transplantation may be beneficial in much the same way that endomyocardial biopsy helps in selecting patients who need augmented immunosuppression.

Dobutamine stress echocardiography (DSE) is rapidly emerging as the noninvasive test of choice in the screening for allograft CAD (10,11) and in predicting outcome in heart transplant recipients (12). However, it is unclear whether the wall motion abnormalities induced during DSE have the same implications early after transplantation. To the best of our

From the Gunderson Lutheran Heart Institute, LaCrosse, Wisconsin; and *McGuire Veterans Affairs Medical Center, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia. This study was presented in part at the 69th Scientific Sessions of the American Heart Association, New Orleans, Louisiana, November 1996 and published in abstract form (Circulation 1996;94 Suppl I:I-25, I-649). It was supported in part by funds from the Veterans Affairs Research Service, Washington, D.C.

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Address for correspondence: Dr. Kwame O. Akosah, Gunderson Lutheran Heart Institute, 1836 South Avenue, LaCrosse, Wisconsin 54601. E-mail: kakosah@gc.gundluth.org.

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Abbreviations and Acronyms

CAD = coronary artery disease
DSE = dobutamine stress echocardiography
ECG = electrocardiogram, electrocardiographic
ISHLT = International Society of Heart and Lung Transplantation
LAD = left anterior descending coronary artery
LVEF = left ventricular ejection fraction
MI = myocardial infarction

knowledge, DSE has not been used in patients with a new transplant (<2 years) in a serial fashion to assess the early development of CAD.

Accordingly, the objectives of this study were 1) to evaluate the ability of serial DSE to predict the eventual development of angiographic CAD; 2) to relate the significance of persistent, inducible wall motion abnormalities with outcome in heart transplant recipients up to 2 years after transplantation; and 3) to assess the safety of DSE soon after heart transplantation.

Methods

Study group. The study included consecutive patients undergoing heart transplantation at our institution. There were 32 new heart transplant operations performed from January 1992 through May 1996. Four patients died early. Of the remaining 28 patients, four had follow-up in their respective home towns; therefore, DSE studies were not done. One patient developed mediastinitis and had an operation with a mediastinal flap, making echocardiographic imaging difficult. Another patient did not undergo serial echocardiographic studies owing to prolonged post-transplant clinical instability. Thus, 22 patients comprised the final study group and were enrolled in this longitudinal study.

All patients were on a standard immunosuppression regimen with cyclosporin (6 mg/kg body weight per day), azathioprine (2 mg/kg per day) or prednisone (0.4 mg/kg per day), or a combination of these. Two patients received OKT3 and one other had antithymocyte globulin for prophylaxis. Acute rejection was treated with augmented immunosuppression with steroids. No patient had any medication changes made for the purpose of the study. Lipid profile was checked on all patients at 1, 12 and 24 months.

According to the study design, patients underwent serial DSE along with their routine post-transplant diagnostic evaluation. DSE was performed at the time of their endomyocardial biopsy or diagnostic cardiac catheterization. The tests were done within 24 h of each other. The study was approved by the Committee on the Conduct of Human Research of the Virginia Commonwealth University and the Research Committee of the McGuire Veterans Affairs Medical Center.

The timing of the first DSE study was decided by the transplant team. Whenever it was decided that the patient was stable enough to participate in the study, DSE was performed at the time of endomyocardial biopsy. The mean time of the first DSE study was 2 months (range 16 days to 4 months) after heart transplantation. Coronary angiography was done within 1 year of transplantation in all patients.

Cardiac catheterization. Diagnostic cardiac catheterization was performed in all patients as part of the routine post-transplant evaluation. No patient underwent cardiac catheterization based on the results of the stress echocardiogram. Each patient had at least one diagnostic cardiac catheterization performed. Selective coronary angiography was performed in a standard fashion after administration of intravenous nitroglycerin. Coronary stenoses were graded and classified according to a previously published scheme by Gao et al. (13). Focal epicardial lesions were interpreted as significant if the lumen stenosis was >50% in at least two orthogonal views. Small-vessel and diffuse disease without discrete lesions were classified as such. All interpretations were done by two experienced independent reviewers who had no knowledge of the results of the other diagnostic tests.

Endomyocardial biopsy. Endomyocardial biopsy was performed by introducing the biopsy forceps into the right ventricle through a long sheath. Approximately three to four pieces of myocardial tissue were sampled during each procedure. The schedule for surveillance endomyocardial biopsies at our institution is as follows: weekly for the first month, biweekly for the next month, monthly for 6 months and every other month to 18 months. After this period biopsies are taken every 3 months up to 2 years. The biopsy specimens were analyzed by experienced pathologists who had no knowledge of the patients' clinical data. Acute cellular rejection was graded according to the International Society of Heart and Lung Transplantation (ISHLT) criteria (14). For the purpose of this study, only grade ≥2 was considered as significant allograft rejection.

Dobutamine infusion protocol. All patients were asymptomatic and studied in the postabsorptive state after a 12-h fast. In all cases DSE was performed within 24 h of either the endomyocardial biopsy or the diagnostic cardiac catheterization. Dobutamine infusion was begun after baseline data, including a 12-lead electrocardiogram (ECG), blood pressure, heart rate and echocardiographic images, were obtained. We used the 5-min stages of 5-, 10-, 20-, 30- and 40-μg/kg per min dobutamine infusion. Our protocol called for early termination in case of ECG changes ≥2 mm ST segment depression, symptomatic hypotension or intolerable symptoms (10).

Two-dimensional echocardiography. Two-dimensional echocardiography was performed with a 2.5- or 3.5-MHz transducer and commercially available scanner (Hewlett-Packard, Sonos 1500 model 77035A). Echocardiographic images were acquired at baseline and during the last 2 min of each infusion stage. Images were obtained in the left lateral decubitus position and recorded on videotape. Four standard views were obtained: parasternal long- and short-axis views and apical four- and two-chamber views. Images were digitized and stored on a hard drive controlled by a computer workstation

(Nova Microsonics Image Vue). Digitized images were transferred to optical drive for off-line analysis.

Echocardiographic image analysis. Representative images of each view were stored in real-time into cine loops at baseline, 5 μg/kg per min, peak dobutamine infusion and recovery. For this study, wall motion was read qualitatively as normal, hypokinesia, akinesia or dyskinesia. Different myocardial segments were assigned to their respective coronary distribution. For instance, segments in the anterior, apex, anteroseptal and mid-septal positions were assigned to the left anterior descending coronary artery (LAD). Segments in the posterior and lateral positions were assigned to the left circumflex coronary artery and those in the inferior position to the right coronary artery.

Wall motion was analyzed by two experienced echocardiographers who had no knowledge of the clinical data, including coronary angiograms and biopsy results. Regional wall motion was determined by simultaneous comparison of the cine loops. A normal response to dobutamine was defined as augmentation of baseline systolic wall motion. A positive response was defined as a lack of augmentation, worsening of baseline segmental abnormality or development of a new wall motion abnormality.

Necropsy analysis. Heart specimens from patients who died were reviewed. Multiple sections from both ventricles as well as from the coronary arteries were examined. The cause of death was ascertained as cardiac or noncardiac depending on the pathologic observations.

Statistical analysis. All data in the text and tables are expressed as the mean value ± SD. Differences between mean values were analyzed by the Student *t* test. The relation between abnormal tests and outcome was evaluated by using the Fisher exact test. Event-free survival data were examined using the Kaplan-Meier method and the Cox proportional hazards model. Differences in survival among the groups were determined by the Wilcoxon sign-rank test. The cutoff for significance for all analyses was set at $p \leq 0.05$.

Results

General characteristics. This longitudinal study involved 22 asymptomatic new heart transplant recipients. All of the study patients were men (average age 49.7 ± 9.6 years). The donor age was 28.1 ± 11.3 years (range 14 to 55). The mean donor heart ischemic time was 152 ± 31 min (range 82 to 238). Pretransplant diagnoses included ischemic cardiomyopathy (n = 10), dilated cardiomyopathy (n = 11) and valvular heart disease (n = 1). At the time of the first study, the mean cholesterol level was 197 ± 46 mg/dl and the left ventricular ejection fraction (LVEF) was 55 ± 4%. Table 1 gives the baseline demographic data of the study group. All 22 patients were receiving immunosuppressive therapy with two or three agents. Two patients had received OKT3 monoclonal antibody and another patient antithymocyte globulin within the first 3 months of heart transplantation. The overall results of DSE, the cardiac events and their time of onset are summarized in Table 2. Table 3 describes the comparative demographic data in patients with and without cardiac events.

Table 1. Baseline Demographic Data of Study Patients

Recipient age (yr)	49.7 ± 9.6
Donor age (yr)	28.1 ± 11.3
Etiology of heart failure	
Ischemic cardiomyopathy	9
Dilated cardiomyopathy	12
Valvular heart disease	1
Ischemic time (min)	152 ± 31
Serum cholesterol (mg/dl)	197 ± 46
Baseline LVEF (%)	55 ± 4

Data presented are mean value ± SD or number of patients. LVEF = left ventricular ejection fraction.

Dobutamine stress echocardiograms. There were a total of 91 serial DSE studies performed in the 22 study patients (Table 2). In seven patients (32%), all serial DSE images were interpreted as normal (Group 1). In these seven, there were no instances of inducible wall motion abnormalities on any of their DSE studies. Four patients (18%) had dobutamine-induced wall motion abnormalities that were nonpersistent (Group 2). These patients developed inducible abnormalities at one time or another, which resolved on subsequent testing. In other words, although there had been inducible abnormalities on some tests during the study, these abnormalities

Table 2. Dobutamine Stress Echocardiographic Results, Cardiac Events, Number of Rejection Episodes and Follow-Up Time in 22 Male Study Patients

Pt No./ Age (yr)	Serial DSE	No. of Rejection Episodes	Cardiac Event	Follow-Up Time (months)
1/54	Persistent	2	None	17
2/44	Normal	0	None	18
3/54	Persistent	0	Small-vessel CAD	46
4/62	Persistent	1	Small-vessel CAD/death	14
5/57	Persistent	0	LAD bridging	16
6/44	Persistent	0	60% stenosis of LAD/death	28
7/36	Persistent	1	Diffuse CAD	48
8/56	Persistent	0	100% stenosis of LAD	8
9/36	Persistent	0	MI (normal coronary arteries)	4
10/54	Persistent	1	60% stenosis of LAD/death	11
11/47	Persistent	1	None	28
12/57	Persistent	0	None	50
13/59	Transient	2	None	31
14/48	Transient	0	None	44
15/23	Transient	0	None	49
16/54	Normal	0	None	22
17/48	Normal	2	None	42
18/46	Normal	0	None	25
19/48	Normal	0	None	48
20/55	Normal	0	None	33
21/47	Normal	0	None	42
22/38	Transient	3	None	5

CAD = coronary artery disease; DSE = dobutamine stress echocardiography; LAD = left anterior descending coronary artery; MI = myocardial infarction; Pt = patient.

Table 3. Comparative Demographic Data in Patients With and Without Cardiac Events

	Event Group	No Event Group	p Value
Donor age (yr)	22 ± 11	26.5 ± 11	NS
Recipient age (yr)	56.0 ± 11	49.5 ± 8.3	NS
Ischemic time (min)	146 ± 18	160 ± 44	NS
Time since transplantation (mo)	16 ± 15	42 ± 11	0.05
Cholesterol (mg/dl)	191 ± 21	224 ± 29	0.007
Baseline LVEF	55 ± 3	55 ± 4	NS

Data presented are mean value ± SD. LVEF = left ventricular ejection fraction.

normalized at a later time during the course of the study. Moreover, in these four patients with nonpersistent wall motion abnormalities, the magnitude of the inducible abnormalities generally followed a decreasing trend toward normalization. In contrast, the other 11 patients (50%) developed inducible abnormalities that remained persistent from test to test (Group 3). This means that once they developed inducible abnormalities, subsequent tests remained abnormal. In general, both the magnitude and threshold level of inducible ischemia worsened. For instance, it was not uncommon for inducible abnormalities to progress toward rest regional dyssynergy.

One patient among the group with no abnormalities on serial testing (Group 1) was treated for acute rejection on two occasions. Of the four patients with transient, inducible abnormalities (Group 2), two were treated on three occasions for suspected allograft rejection. In one of these two patients, despite ISHLT grade 0 rejection on endomyocardial biopsy, the rest LVEF had decreased to 42% from 70% on the radionuclide scan. There were four patients who were treated for rejection in the group with persistent abnormalities (Group 3), including one with a negative biopsy.

Safety and side effects of DSE. Ninety-one DSE studies were done in 22 patients. No major complication occurred at any time during the DSE studies. No patient developed angina. ECG changes suggestive of ischemia occurred once. Commonly reported side effects in this cohort included tremor (7%), flushing (5%) and headache (2%). In addition, dizziness occurred in 4% and shortness of breath in 2.4%. One patient developed a three-beat run of nonsustained ventricular tachycardia.

Endomyocardial biopsy. Acute cellular rejection requiring augmented immunosuppressive therapy was diagnosed eight

Table 4. Number of Rejection Episodes and Angiograms and Date of Event in Three Subgroups of Patients

Pt No.	No. of Rejection Episodes			Tx Date	Date of First DSE	No. of DSE Studies	No. of Angiograms	Date of Event	Cholesterol (mg/dl)		Triglycerides (mg/dl)	
	During Study Period	Before Enrollment	Treated but Negative Biopsy						1 Month	12 Months	1 Month	12 Months
Patients (n = 11) With Persistent Abnormalities on Stress Echocardiogram												
1	0	2	0	4/16/95	7/19/95	3	1	NE	215	195	253	195
2	0	0	0	5/8/92	11/4/92	3	3	3/8/96	178	241	378	80
3	1	0	0	1/1/94	6/2/94	3	1	3/24/95	210	181	83	58
4	0	0	0	6/9/94	8/8/94	3	1	10/10/95	329	184	328	106
5	0	0	0	8/21/93	1/19/94	7	2	12/5/95	304	225	191	149
6	0	0	1	2/27/93	3/1/93	4	3	2/14/96	229	224	246	303
7	0	0	0	7/21/95	9/21/95	5	1	3/11/96	171	192	317	135
8	0	0	0	7/22/94	4/29/94	3	1	11/20/94	271	85	243	85
9	1	0	0	2/19/93	7/15/93	6	1	5/12/94	220	256	99	256
10	1	0	0	5/4/94	5/20/94	4	2	NE	232	254	141	424
11	0	0	0	7/7/92	12/11/92	4	3	NE	181	159	177	276
Patients (n = 4) With Transient Abnormalities on Stress Echocardiogram												
12	0	0	0	2/13/94	4/15/94	6	2	NE	217	193	65	99
13	0	0	0	1/28/93	8/12/93	6	3	NE	179	255	114	362
14	0	0	0	8/14/92	12/21/92	3	3	NE	247	364	133	461
15	0	0	0	3/18/93	6/21/93	9	3	NE	262	293	205	247
Patients (n = 7) With Normal Stress Echocardiogram												
16	0	0	2	3/11/95	3/1/96	1	1	NE	257	217	68	224
17	0	0	0	11/22/94	1/3/95	3	2	NE	216	202	138	351
18	0	0	0	8/30/94	11/4/94	3	2	NE	216	248	431	571
19	0	0	0	9/9/92	12/4/92	4	3	NE	275	235	345	115
20	0	0	0	3/29/93	6/29/93	7	3	NE	222	193	68	125
21	0	0	0	12/21/93	4/1/94	2	3	NE	260	274	124	75
22	0	0	0	5/17/96	6/17/96	2	1	NE	205	203	115	194

NE = no event; Tx = transplantation; other abbreviations as in Table 2.

Figure 1. Histologic study of the coronary arteries of one of the study patients. Note the presence of myointimal hyperplasia involving all of the coronary arteries, proximal **(A)** and distal **(B).** Also note branch vessel occlusion **(arrow)** and the absence of significant lipid plaques. Hematoxylin-eosin ×5, reduced by 35%.

times in five patients during the study. One additional patient had been treated for cellular rejection two times before his first enrollment into the study. Two other patients were treated three times for suspected acute rejection, although their subsequent biopsies demonstrated ISHLT grade 0 rejection. There were significant reductions in the LVEF in these two patients, which resolved after therapy. Table 4 gives the details of biopsy relative to DSE and coronary angiographic studies.

Diagnostic cardiac catheterization. There were a total of 45 diagnostic cardiac catheterization procedures, with coronary angiography performed in 22 patients. Each patient had at least one cardiac catheterization done (mean 2, range 1 to 3). Coronary angiography revealed development of CAD in seven patients (32%). One patient had bridging of the mid LAD. Three others had significant narrowing of the LAD (100% in 1, 60% in 2), whereas three had diffuse small-vessel disease. The mean time from transplantation to detection of angiographic disease or cardiac event was 16 ± 15 months (range 4 to 48). Table 2 gives a complete summary of the test results. In addition, Table 4 gives the relative number of angiograms and biopsies and their relation to wall motion abnormalities in the three groups of patients.

Follow-up observations. The mean duration of follow-up for the entire group was 32 ± 11 months (range 5 to 50). The end points were death, myocardial infarction (MI) and presence of angiographic CAD. During this period, 8 (36%) of 22 patients developed cardiac events. One patient had an acute MI, as manifested by elevation of cardiac enzymes and ECG changes. Diagnostic cardiac catheterization in this patient was interpreted as normal. Seven (32%) of 22 patients eventually developed angiographic CAD. Angiographic disease in the seven patients included diffuse small-vessel disease in three and LAD stenosis in the other four (bridging in 1, total in 1, 60% in 2). There were three cardiac deaths (14%). One of the three patients with diffuse disease on the initial angiogram died. Necropsy evaluation of the heart revealed massive MI involving ~75% of the entire left ventricle. The coronary anatomy of this patient confirmed severe three-vessel disease. Representative light microscopic findings are depicted in Figure 1. The other two patients who died demonstrated LAD disease. The diagnosis was made at autopsy in one patient. The mean duration from transplantation to end point was 16 ± 15 months (range 4 to 48) compared with a mean follow-up period of 42 ± 11 months (range 5 to 50) ($p < 0.05$) in those without a cardiac event. There were no significant differences between the patients without an event and those with an event in terms of donor age (26.5 ± 11 vs. 22 ± 11 years), recipient age (49.5 ± 8.3 vs. 56 ± 11 years) or ischemic time (160 ± 43.5 vs. 146 ± 17.9 min). Similarly, there was no difference in the baseline LVEF (55 ± 4% vs. 55 ± 3%) (Table 3). No event or coronary disease occurred in either the group with completely normal stress echocardiograms or the group with transient abnormalities (Groups 1 and 2). In contrast, 8 (73%) of the 11 patients with persistently abnormal DSE studies developed angiographic CAD or MI, including three deaths (27%). In other words, all clinical events and angiographic disease developed only in patients with persistent abnormalities on serial DSE studies. The event rate for each of the three groups is illustrated in Figure 2. In Group 3 patients who demonstrated persistent wall motion abnormalities on serial testing, the event rate was markedly increased and was related to allograft CAD. The observed differences in the development of angiographic CAD, death or MI (8 of 11 vs. 0 of 11 patients) was significant ($p = 0.001$). At an alpha level of 0.05, the power to detect the observed differences was calculated at 94%.

Serum cholesterol at 1 month after transplantation was lower in patients with events than in those without events (191 ± 21 vs. 227 ± 29 mg/dl, $p < 0.0070$). The serum cholesterol level at 1 year (246 ± 51 vs. 234 ± 52 mg/dl) and 2 years (228 ± 32 vs. 227 ± 44 mg/dl, p = NS) was similar for the

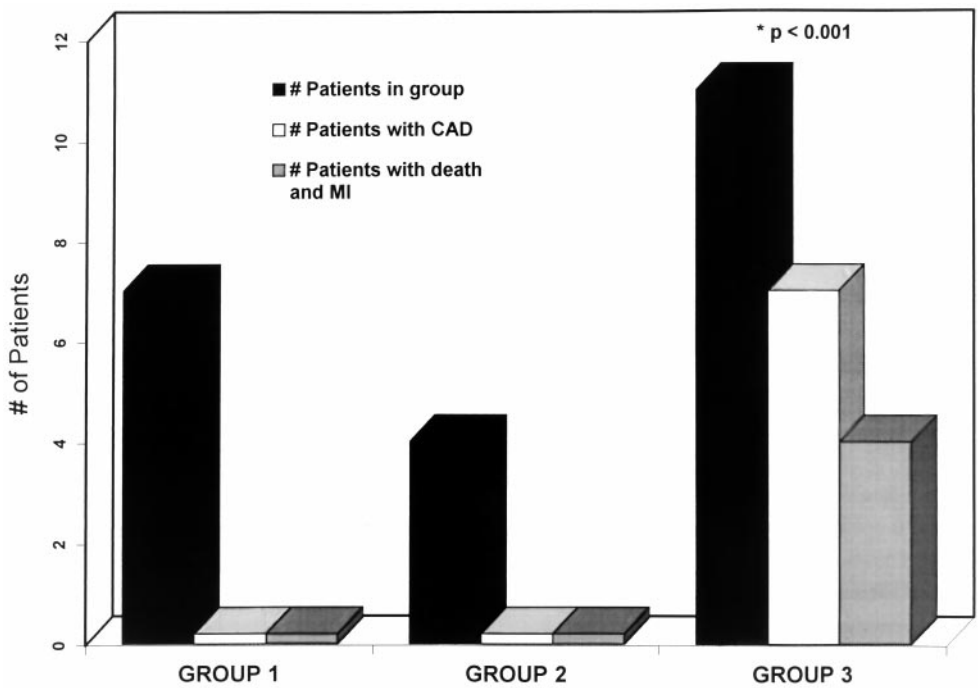


Figure 2. Bar graph illustrating the event rate in the three subgroups of patients. The number of patients in each group is represented by the **solid bar.** The number of patients who developed angiographic CAD is represented by the **open bar,** and the **gray bar** represents patients with cardiac events. Note that angiographic CAD, death and MI occurred only in the group with persistent, inducible wall motion abnormalities.

patients with an event and those without an event. Although the initial cholesterol level was lower in the group with events, the mean change in total cholesterol was significantly higher (55 ± 53 vs. 7.2 ± 56.6 mg/dl, $p < 0.04$). Compared with the group without an event, neither serum triglyceride levels at baseline (1 month after transplantation), 1 year and 2 years nor changes in the mean levels were significantly different between the group with events and the group without events.

Patient outcome. The prognostic significance of the data is displayed by the Kaplan-Meier curves shown in Figures 3 and 4. The analysis was done by comparing Group 3 with Groups 1 and 2. There were significant differences in all events or acute MI and death combined. The cumulative risk of developing angiographic CAD was significantly higher in those patients who had persistently abnormal stress echocardiograms. The survival rate was also significantly decreased for this group. The rate of death and MI was 36% for this group. In contrast, the event-free survival rate for patients with either normal stress echocardiograms or transient abnormalities was 100% (Fig. 3). We examined the effect of recipient and donor age, serum cholesterol level, ischemic time, pretransplant diagnosis and baseline LVEF on survival by using multivariate analysis. None of these variables had any effect on the outcome. Only the persistent, inducible wall motion abnormalities on serial testing emerged as independent predictor of outcome.

Figure 3. Kaplan-Meier survival distribution showing freedom from all events (CAD, death and MI) as a function of time. Note that event-free survival is markedly decreased for the patients with persistent abnormalities on serial DSE (**lower curve**). In contrast, there was absolute freedom from events in those patients with normal DSE studies and transient abnormalities (**upper curve**), $p < 0.002$.

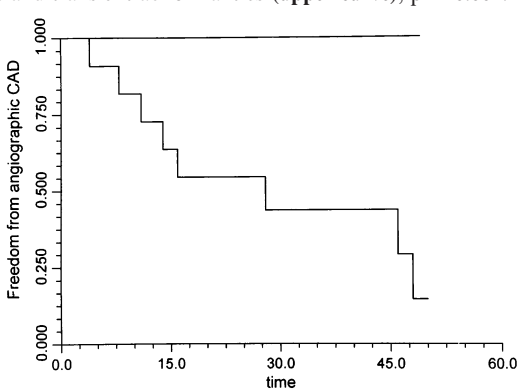
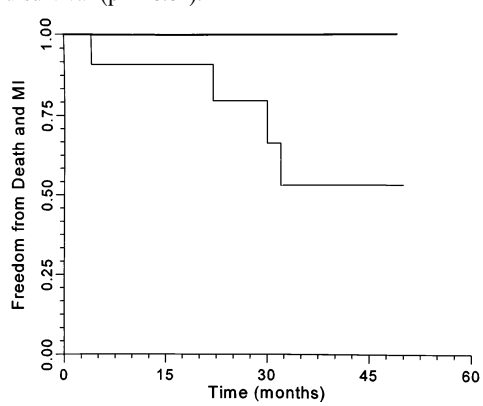


Figure 4. Kaplan-Meier plot illustrating freedom from death and MI. **Upper curve** represents patients with normal DSE studies and those with transient abnormalities. **Lower curve** is the survival distribution for the group with persistent abnormalities on DSE and shows decreased survival ($p < 0.02$).



Discussion

Although the initial success rate is high (15), the long-term outcome of heart transplant recipients is limited by accelerated CAD (6). Accelerated CAD in heart transplant recipients is difficult to diagnose, mainly because of the diffuse nature of the disease. Our current understanding is evolving through the studies of intracoronary ultrasound imaging, coronary endothelial functional assessment, angiograms and a variety of cardiac noninvasive tests. Taken together, the studies suggest that the coronary disease process starts early, may involve small vessels and then progresses rapidly.

Clinically, there are no specific signs and symptoms, and the clinical presentation is often late and atypical (16). Histologically, the disease differs from typical atherosclerosis in that the immune-mediated injury may be the primary initiating event causing myointimal hyperplasia of smooth muscle cells and subsequent lipid deposits that eventually compromise the arterial lumen (17). The limitations of coronary angiography (18) and standard noninvasive tests have been demonstrated in many recent studies (2,6–8). It is important to ask questions as to whether there are any potential risk factors that may modify the disease process and outcome. A reasonable first step in addressing some of these issues must include developing a noninvasive test that is capable of identifying patients at risk for developing angiographic CAD and subsequent cardiac events. In this regard, the significance of the current study is threefold: first, the development of wall motion abnormalities that are persistent on serial testing identifies patients at risk for poor outcome. Second, inducible wall motion abnormalities early after transplantation are predictive of the eventual development of angiographic CAD. Third, the DSE protocol is feasible and safe soon after heart transplantation. Serial DSE early after transplantation can be performed without significant adverse consequences.

Although DSE has emerged as a reliable screening test for allograft CAD (10,11), the experience to date has been limited to patients with long-term transplants (>3 years), by which time the disease is usually extensive and treatment options are limited. We are unaware of any previous experience of serial DSE in heart transplant recipients. This report extends our previous observations on the usefulness of this simple, noninvasive test in patients early after transplantation. The safety profile documented previously (6,10–12) and in the current study is reassuring. In the current study, no patient had any major side effects. Nonsustained ventricular tachycardia of three beats occurred only one time during 91 tests. Minor side effects included headache, dizziness and dyspnea.

The relation between inducible ischemia and eventual development of CAD is of great interest, although the mechanism(s) remain unknown. In the patient with a new transplant, several factors, including rejection, postischemic myocardial necrosis and infections, are known to cause left ventricular dysfunction (1–3). Previous reports involving only rest abnormalities suggest that rest wall motion abnormalities or left ventricular dysfunction do not lead to poor outcomes (3). We found only a small group of patients with normal rest systolic function in whom the ischemic response to dobutamine provocation developed at some time during serial testing. This group of patients with transient abnormalities had no evidence of angiographic disease on routine annual angiograms, and their outcomes were similar to those with a completely normal response. Unfortunately, the mechanism(s) of this transient, inducible dysfunction cannot be answered by the current study. The extent to which undetected cellular or vascular rejection may have contributed to the transient abnormalities is unknown. For reasons unclear, it appears that some transplant recipients develop transient, inducible ischemia in response to dobutamine stress. In contrast, a high percentage of patients with inducible abnormalities that are reproducible on serial tests eventually develop angiographic disease. The wall motion abnormalities in this group are progressive, become more extensive and develop at lower dobutamine dosages on serial testing and may eventually progress to rest abnormalities.

The early disease is usually beyond the resolution of routine angiography, and by the time stenosis of the epicardial vessels is detectable, it is often advanced. In fact, this is consistent with early reports of endothelial function (19), coronary flow reserve (20) and intravascular ultrasound imaging (21,22), which all show that significant abnormalities are present in the setting of "normal" coronary angiograms. The results of this study show that the prognosis in patients with persistent, inducible abnormalities is poor. These observations suggest that DSE may have an important role in the routine follow-up evaluation of heart transplant recipients. The current report, taken together with our previous findings (12) of the prognostic significance of DSE in patients with heart transplants >5 years old, indicates that abnormal DSE studies imply a poor outcome in any transplant recipient with persistent, inducible abnormalities. Furthermore, a negative DSE test suggests a virtual absence of angiographic disease and implies a good outcome regardless of the time since transplantation.

Clinical implications. The experience with DSE in new heart transplant recipients is limited. For this reason we believe it is premature to make any specific recommendations at this time. However, based on the consistency of the results in patients with long-term transplants and results of this study, we offer the following suggestions. Patients who develop dobutamine stress–induced regional wall motion abnormalities may need close monitoring and further studies, including coronary angiography and intravascular ultrasound imaging, to define the functional and anatomic severity of CAD. The prognosis in these patients is poor despite the absence of focal epicardial lesions on coronary angiography, which, in fact, may represent advanced disease. Patients with persistent abnormalities on serial DSE may need to be targeted for aggressive risk factor interventions and close surveillance for possible early consideration of retransplantation. In the light of increasing data showing the reliability of DSE in screening for allograft CAD, it may be argued whether routine coronary angiography should be performed annually, as is presently done in most centers.

The current study involves a relatively small number of patients in one center, which provides important clues that DSE may be of significant value in the screening and routine management of heart transplant recipients. As the experience of this diagnostic test becomes more widespread, it may allow us to reserve angiography for patients with abnormal noninvasive tests and for those who present with symptoms, especially if they are considered candidates for interventional therapy.

Study limitations. In this study we evaluated the development of CAD with angiography. It is well established that intravascular ultrasound imaging is a far more sensitive method to detect allograft CAD (21,22). It is conceivable that the use of intravascular ultrasound imaging may have identified more patients with allograft CAD. Furthermore, we did not take into account the potential influence of unidentified vascular rejection on inducible wall motion abnormalities observed transiently in Group 1 patients, owing to the fact that we do not routinely perform histopathologic analysis for vascular rejection. The extent to which vascular rejection contributes to the development of allograft CAD, therefore, cannot be determined from our study.

Conclusions. The results of this study demonstrate that it is safe to perform DSE early after heart transplantation in stable asymptomatic patients. We have also shown that abnormal serial DSE studies are strongly predictive of the eventual development of angiographic CAD and identify new transplant recipients at risk for cardiac events. Large studies, preferably multicenter in design, incorporating intracoronary ultrasound methods may be invaluable in further defining the role of DSE in the screening and management of accelerated CAD in the heart transplant recipient.

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